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REMARKS

Claims 1-29 and 45-73 are pending in this application. Claims 30-44 were previously cancelled in response to the December 17, 2001 Restriction Requirement. Claims 1 and 45 have been amended. Support for these amendments can be found at least on pages 20, 21, 25, and 35-42. Applicant respectfully submits that no new matter has been added by way of these amendments.

Claims 1-29 and 45-73 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention.

Applicant explicitly defines the phrase "menopause disorder" in the application as filed on page 21, lines 7-15. As Applicant explains, the phrase "menopause disorder" encompasses peri-menopausal conditions as well as post-menopausal conditions. As stated in the application, a "'[p]eri-menopausal condition' refers to a condition that occurs either during menopausal onset, or prior thereto at a time when menopausal onset normally occurs, and either is caused by menopausal onset or has a greater than random coincidence therewith . . . [and] include[s], for example, hot flashes and reduction of bone mass." Applicant respectfully submits that a person of ordinary skill in the art, at the time the present application was filed, would recognize other peri-menopausal conditions that are encompassed by the expression "menopause disorders." (*See e.g.*, U.S. Patent No. 5,908,638). Further, the claims have been amended to better define the invention. Support for the amendments made to claims 1 and 45 is found at least on pages 20, 21, 25, and 35-42. Applicant requests reconsideration and withdrawal of this rejection in view of the amended claims.

Claims 1-29 and 45-73 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Rubin (US Patent 5,059,603), Ebert et al. (US Patent 5,152,997), and Place (US Patent 6,117,446) in view of Langtry et al. (Drugs 1999:57(6): 967-989), Remington's Pharmaceutical Sciences (1990, 18th ed., pages 1305 and 1314), Merck Index (11th ed., 1989, page 821, monograph 5103), Hofman et al. (US Patent 4,563,473), and Atkinson et al. (US Patent 4,442,094).

Applicants disagree and traverse this rejection. Rubin, Ebert et al, and Place in view of Langry et al., Remington's Pharmaceutical Sciences, Merck Index, Hofman et al., and Atkinson et al. do not teach or suggest the claimed invention. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. (MPEP 2143.01 citing In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)).

As it now stands before the Patent Office, claim 1 recites, among other things, a method of treating, preventing or reducing the risk of developing a menopause disorder by administering a menopause disorder effective amount of a pharmaceutically-acceptable sex hormone binding globulin synthesis inhibiting agent in an oral dosage unit, and at least one pharmaceutically-acceptable steroid in a non-oral dosage unit. Claims 2-29 depend directly or indirectly from independent Claim 1.

Claim 45 recites, among other things, a method of treating, preventing or reducing the risk of developing a menopause disorder by administering in a combination therapy a pharmaceutically-acceptable sex hormone binding globulin synthesis inhibiting agent in an oral dosage unit, and at least one pharmaceutically-acceptable steroid in a non-oral dosage unit, wherein the amount of the sex hormone binding globulin synthesis inhibiting agent and the

steroid together make a menopause disorder effective amount. Claims 46-73 depend directly or indirectly from independent Claim 45.

In the Background of the Invention, Rubin discloses that methyltestosterone has been administered subcutaneously or bucally in the past to treat impotence. Rubin then proceeds to teach away from using methyltestosterone in the treatment of impotence because it

> may cause severe toxic effects such as cholestatic jaundice[,] . . . additional pain, lack of complete absorption, and risk of deep and widespread infection. Additionally, long-term administration of [methyltestosterone] may inhibit endogenous testosterone formation and spermatogenesis by suppressing pituitary gonadotropin, resulting in glandular tissue atrophy because of disuse. Rubin, Col. 3, lines 1-11.

Rubin does not teach or suggest a method of treating, preventing or reducing the risk of developing a menopause disorder by administering a menopause disorder effective amount of a pharmaceutically-acceptable sex hormone binding globulin synthesis inhibiting agent in an oral dosage unit, and at least one pharmaceutically-acceptable steroid in a non-oral dosage unit.

Ebert *et al.* teach a transdermal composition including testosterone and a permeation enhancer useful in treating male hypogonadism. However, Ebert *et al.* do not teach or suggest a method of treating, preventing or reducing the risk of developing a menopause disorder by administering a menopause disorder effective amount of a pharmaceutically-acceptable sex hormone binding globulin synthesis inhibiting agent in an oral dosage unit, and at least one pharmaceutically-acceptable steroid in a non-oral dosage unit.

Place recognizes that although androgens are mostly known for causing the masculinizing changes in males during puberty, low levels of androgens are also present in normal females. (See Place, Col.1, lines 17-21). Therefore, Place teaches the administration of an androgenic agent with a progestin and an estrogen in a buccal dosage unit to provide a complete hormone replacement therapy for women. Place does not teach or suggest a method of

treating, preventing or reducing the risk of developing a menopause disorder by administering a menopause disorder effective amount of a pharmaceutically-acceptable sex hormone binding globulin synthesis inhibiting agent in an oral dosage unit, and at least one pharmaceutically-acceptable steroid in a non-oral dosage unit.

Applicant respectfully submits that none of the foregoing references teach or suggest, either alone or in combination, a method of treating, preventing or reducing the risk of developing a menopause disorder by administering a menopause disorder effective amount of a pharmaceutically-acceptable sex hormone binding globulin synthesis inhibiting agent in an oral dosage unit, and at least one pharmaceutically-acceptable steroid in a non-oral dosage unit as required in Claims 1 and 45.

The Examiner, then, cites the following references in arguing the obviousness of various claims that depend from Claim 1 or 45:

Langtry *et al.* teach that sildenafil is an oral therapy for erectile dysfunction.

Remington's Pharmaceutical Sciences teaches that ethanol may be used externally in astringents and anhidrotic lotions and as a solvent to cleanse the skin. Further, it teaches that carboxymethylcellulose sodium may be used in a tablet as a "pharmaceutic acid (suspending agent, tablet excipient or viscosity-increasing agent)."

The Merck Index teaches that isopropyl myristate may be used in topical medicinal preparations where good absorption through the skin is desired.

Hofman *et al.* teach sebum synthesis inhibiting compositions. The compositions may be in a gel form including an alcohol such as 2-propanol or ethanol, gel forming agents including but not limited to Carbopol, and penetration promoting agents including but not limited to isopropyl myristate.

Atkinson *et al.* teach that pharmaceutically acceptable carriers may include, among various other elements, lower alkanols, carboxymethylcellulose, isopropyl myristate, and carbopol.

Neither Langtry *et al.*, Remington's, Merck Index, Hofman *et al.*, nor Atkinson *et al.* teach or suggest, alone or in combination, a method of treating, preventing or reducing the risk of developing a menopause disorder by administering a menopause disorder effective amount of a pharmaceutically-acceptable sex hormone binding globulin synthesis inhibiting agent in an oral dosage unit, and at least one pharmaceutically-acceptable steroid in a non-oral dosage unit. Neither do these references, either alone or in combination, teach the elements of Claims 1 or 45 that are missing from Rubin, Ebert et al., and Place.

Furthermore, there is no motivation to combine the cited references. The Office Action states that "[e]mploying sildenafil with testosterone and methyltestsosterone, which are known to be useful in treating impotence individually, in a method useful for the very same purpose would be *prima facie* obvious." However, the Office Action does not cite any reference showing or suggesting the combination of these elements in the manner recited in Claims 1-29 and 45-73.

In making this unsupported statement, the Office Action is attempting to shift the burden of proof of unobviousness to the Applicant.

The Applicant respectfully submits that the teaching of In re Kerkhoven, 626 F.2d 846, 205 U.S.P.Q. 1069 (CCPA 1980), has been misapplied in determining the obviousness of the present invention. Applicant contends that the appropriate standard to determine obviousness in this case is not found in In re Kerkhoven. The decision in In re Kerkhoven was based upon prior art teachings and the applicant's own admissions. The court noted that the Examiner stated during the proceedings that:

> th[e] process [of the invention] would be suggested by the teachings in Tofflemire [a cited prior art reference] and appellant's admission in the sentence bridging pages 27 and 28 of his brief that 'given the long standing practice of spray drying with a multiplicity of nozzles, the possibility of introducing separate streams to any or all of these separate nozzles would be obvious to anyone of ordinary skill in the art. Id. at 849.

It was also noted that the applicant admitted before the board that a prior art reference "makes detergent compositions by spray drying two detergent slurries of different chemical composition simultaneously in a tower." Id. at 850. The applicant also admitted "that simultaneous spray-drying of two detergent slurries was known." Id.

The present situation is distinguishable from In re Kerkhoven in many respects and is more analogous to In re Geiger, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987). In In re Geiger, three components of the invention had been described in the prior art individually or in partial combination. The prior art did not suggest, however, combining the references and the Applicant made no admissions concerning the prior art.

The Federal Circuit in In re Geiger reversed the decision of the board that: "based upon prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems..., [it] would have been prima facie obvious within the meaning of 35 U.S.C. § 103, to employ these components in combination for their known function...." Id. at 687. The Federal Circuit rejected this conclusion and stated that "the PTO failed to establish a prima facie case of obviousness." Id. The court stated that "obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention absent some teaching, suggestion or incentive supporting the combination." Id. at 688 (citation omitted). The court also stated that "[a]t best, in view of [the cited references], one skilled in the art might find it obvious to try various combinations of these known . . . agents. However, this is not the standard of 35 U.S.C. § 103."

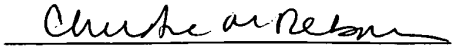
Id. (citations omitted). Although the prior art disclosed the separate components of the claimed new composition, and for the same general use, the court reiterated that a prima facie case was not established "absent some teaching, suggestion or incentive supporting the combination." Id.

In the 35 U.S.C. §103(a) rejection of the present claims, the Office Action has cited no pertinent reference showing or suggesting to one of ordinary skill in the art the motivation to combine the elements in the present claims. The 35 U.S.C. § 103(a) rejection is therefore improper. Further, claims 2-29 depend on the patentability of claim 1 and claims 46-73 depend on the patentability of claim 45. If claims 1 and 45 are patentable, then so to are claims 2-29 and 46-73, regardless of whether other references teach their subject matter. Reconsideration and withdrawal of this 35 U.S.C. §103(a) rejection is requested.

With entry of the above Amendment and in view of the foregoing remarks, it is respectfully submitted that claims 1-29 and 45-73 are in condition for allowance. Also submitted herein, on a separate page titled "Version with Marking to Show Changes Made to the Claims," is a marked up copy of prior pending claims 1 and 45. This page shows the changes made to prior pending claims 1 and 45 and how claims 1 and 45 as amended, now stand before the Patent Office. It is respectfully submitted in view of the foregoing Amendment and Remarks that all of the objections and rejection in the Office Action dated February 8, 2002 have been overcome and should be withdrawn. Accordingly, reconsideration and withdrawal of the outstanding rejections and allowance of claims 1-29 and 45-73 is respectfully solicited. Applicant respectfully requests early and favorable notification to that effect.

Respectfully submitted,

Dated: June 7, 2002

By: 

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Version with Markings to Show Changes Made to the Claims

1. (Amended) A method of treating, preventing or reducing the risk of developing a menopause disorder in a mammal in need thereof, comprising administering to the mammal a menopause disorder effective amount of [an orally deliverable] a pharmaceutically-acceptable sex hormone binding globulin synthesis inhibiting agent in an oral dosage unit, and at least one [of a non-orally deliverable] pharmaceutically-acceptable steroid in a non-oral dosage unit.

45. (Amended) A method of treating, preventing or reducing the risk of developing a menopause disorder in a mammal in need thereof, comprising administering to the mammal in a combination therapy [an orally deliverable] a pharmaceutically-acceptable sex hormone binding globulin synthesis inhibiting agent in an oral dosage unit, and at least one [of a non-orally deliverable] pharmaceutically-acceptable steroids in a non-oral dosage unit, wherein the amount of the sex hormone binding globulin synthesis inhibiting agent and the steroid together make a menopause disorder effective amount.